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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

HARRIS, ALANA M

ART UNIT PAPER NUMBER

1643

DATE MAILED: 10/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/623,813

Applicant(s)

LI ET AL.

Examiner

Alana M. Harris, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 26 July 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 11,12,14-23 and 38-55 is/are pending in the application.
- 4a) Of the above claim(s) 11,12,14-23,43,44 and 50 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 38-42,45-49 and 51-55 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|--|
| <p>1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)</p> <p>2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)</p> <p>3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>01/20/2004; 12/17/2004</u>.</p> | <p>4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.</p> <p>5) <input type="checkbox"/> Notice of Informal Patent Application</p> <p>6) <input type="checkbox"/> Other: _____.</p> |
|---|--|

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group XVII (claims 38-42 and 45-49) in the reply filed on July 26, 2006 is acknowledged. The traversal is on the ground(s) that there is sequence similarity between SEQ ID NO: 86 and 85 and they are both Dnmt3a2 polypeptides. This is found persuasive and consequently Groups XVI, XXII and XXIII will be examined as well.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 11, 12, 14-23 and 38-55 are pending.

Claim 13 has been cancelled.

Claims 11, 12, 14-23, 43, 44 and 50, drawn to non-elected inventions are withdrawn from examination.

Claims 38-42, 45-49 and 51-55 are examined on the merits.

Priority

3. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 112 as follows: while support for SEQ ID NO: 86 has been found in 09/720,086 (filed July 23, 2001), however it is not of record in PCT/US99/14373 (filed June 25, 1999), nor the provisional applications, 60/093, 993 (filed July 27, 1998) and 60/090,906 (filed June 25, 1998). SEQ ID NO: 86

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shares 99.4% sequence identity to an amino acid sequence of 912 amino acids found in Figure 2C; the drawings on page 19 of 36; and attached database sheet. Consequently, Applicants are afforded the priority date, July 23, 2001.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 38, 42 and 45-49 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement commensurate with the scope of the claimed invention. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Claim 38, sections c and d are essentially drawn to polynucleotide sequences that are complementary to polynucleotide sequences that encode SEQ ID NO: 85 (ATCC Deposit No. PTA-4611) and SEQ ID NO: 86 (ATCC Deposit No. PTA-4610) and those sequences that are at least 95% identical to polynucleotides that encode the full length amino acid sequences, SEQ ID NO: 85 and SEQ ID NO: 86. The remainder of the claims read on inserting the sequences of sections c and d into recombinant vectors and host cells for the production and expression of *de novo* DNA cytosine methyltransferase polypeptides. The specification while being enabling for polynucleotide

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sequences that encode full length *de novo* DNA cytosine methyltransferase polypeptides, SEQ ID NOS: 85 and 86, does not reasonably provide enablement for complements of the said polynucleotides. A polynucleotide sequence that is complementary to the sequences listed in sections a-c of claim 38 reads on fragments and not a full length polynucleotide sequence. Moreover, these complements do not read on full length complements capable of expression of full length proteins, *de novo* DNA cytosine methyltransferase polypeptides. A complement of the coding strand packaged into an expression vector will not sufficiently provide a full length product. There is no guidance as to how to make these divergent sequences. The products of these complements may not encode polypeptides that possess function and be commensurate with the functions of the native protein. These complements placed in a recombinant expression system may not encode polypeptides at all and at best may not maintain the activities proposed in the specification. According to the specification these polypeptides are capable of methylating C5 in cytosine moieties in nonmethylated DNA, see page 22, section 0066. Since the amino acid sequence of a polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar activity requires a knowledge of and guidance with regard to which amino acid or acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved and detailed knowledge of the ways in which the protein's structure relates to its function. The specification provides essentially no guidance as to what polynucleotide

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sequences other than those that encode full length proteins are able to be implemented in a recombinant expression system to produce a de novo DNA cytosine methyltransferase polypeptide. The true fact of the state of the art in peptide chemistry is expressed succinctly in the accompanying Lazar article (Molecular and Cellular Biology 8(3): 1247-1252, March 1988/ IDS reference AT, submitted June 20, 2004). This article presents data that substantiates the fact that the introduction of mutations in an amino acid sequence will yield products with different biological activity from the wild type protein. Accordingly, polynucleotides, which are distinct and have significantly reduced sequence homology to wild-type polynucleotides will not yield polypeptides with methyltransferase activity.

From the discussion above, it is clear that the predictability of changes to the amino acid sequence is practically nil as far as biological activities are concerned. The specification fails to provide sufficient guidance to enable one of ordinary skill in the art to make and use the claimed nucleic acids in a manner reasonably correlated with the broad scope of the claims. Without such guidance, the effectiveness of complements to encode full length proteins is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue.

6. Claims 51-55 are rejected under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure without complete evidence either that the claimed

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biological materials are known and readily available to the public or complete evidence of the deposit of the biological materials.

The specification lacks complete deposit information for the deposit of the polypeptides contained in ATCC Deposit No. PTA-4610 and PTA-4611 listed in claim 51. It is not clear that the molecules are known and publicly available or can be reproducibly isolated from nature without undue experimentation. Exact replication of a plasmid is an unpredictable event. It is unclear that one of skill in the art could derive molecules identical to those claimed. Undue experimentation would be required to screen all of the possible cell lines to obtain the claimed plasmids. Because one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed in the absence of the availability of the claimed plasmids, a suitable deposit for patent purposes, evidence of public availability of the claimed plasmids or evidence of the reproducibility without undue experimentation of the claimed plasmids, is required.

If the deposit is made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository is required. This requirement is necessary when deposits are made under the

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provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State. If the deposit is not made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR 1.801-1.809 regarding availability and permanency of deposits, assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request:

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application:

(c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become nonviable or non-replicable.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. Additional means for completing the record is required. Applicant may submit a copy of the contract

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with the depository for deposit and maintenance of each deposit to aid in obviating the instant rejection.

If deposits are made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the cell line described in the specification as filed is the same as that deposited in the depository, stating that the deposited material is identical to the biological material described in the specification and was in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 51-55 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Applicants assert in the Remarks, filed July 26, 2006, page 2, 1st paragraph that the polynucleotide sequences of Groups XXII and XIII encode mouse and human Dnmt3a2, respectively. Claim 51 lists the acronym, Dnmt3a2 for the mouse polypeptide corresponding to ATCC Deposit No. PTA-4611 (SEQ ID NO: 85) and the acronym, DNMT3A2 for the human polypeptide

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corresponding to ATCC Deposit No. PTA-4610 (SEQ ID NO: 86). It is not clear which acronyms are properly identifying the claimed subject matter because of the disparity presented in the Remarks and the claim language. Applicants are requested to clarify the acronyms and their corresponding ATCC numbers and SEQ ID numbers.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

10. Claims 38, 39, 41, 42, 45-49, 51 and 53-55 are rejected under 35 U.S.C. 102(b) as being anticipated by Okano et al. (Nat. Genet. 19(3): 219-220, 1998/ IDS reference AR, submitted December 17, 2004), as evidenced by Accession number AFO68625. Okano discloses a polynucleotide sequence that is 100% and 98% sequence identical to polynucleotide sequences, which encode SEQ ID NO: 85 (ATCC Deposit No. PTA-4611) and SEQ ID NO: 86 (PTA-4610), respectively, see attached database sheet. This sequence is referenced as Dnmt3a (4,192 base pairs), see page 219, 2nd column. Dnmt3a transcripts were

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expressed in embryonic stem (ES) cells using baculovirus expression vectors and were able to methylate DNA substrates, see page 219, 3rd column; and page 220, first paragraph of column 1.

11. Claims 38, 40-42, 51 and 53-55 are rejected under 35 U.S.C. 102(b) as being anticipated by Xie et al. (Gene 236: 87-95, 1995/ IDS reference AR, submitted January 20, 2004), as evidenced by Accession number AF067972. Xie discloses a polynucleotide sequence encoding a polypeptide, SEQ ID NO: 86 (PTA-4610) and a polynucleotide sequence at least 95% identical to a polynucleotide sequence, which encodes SEQ ID NO: 85 (ATCC Deposit No. PTA-4611), see attached database sheets and Figure 1 on page 89, DNMT3A sequence beginning at amino acid residue 201, see middle of that line. The DNMT3A sequence was expressed in both normal tissues and tumor cell lines, see page 92, section 3.4 and Figure 6 on page 94.

12. Claims 38, 40-42, 45-49, 51 and 53-55 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent Application Publication number 2003/0083292 A1 (effective filing date May 11, 2001). Sequence 2 of the patent application publication encodes a polypeptide comprising amino acid residues 1-689 of SEQ ID NO: 86 (PTA-4610) and a polynucleotide sequence at least 95% identical to a polynucleotide sequence, which encodes SEQ ID NO: 85 (ATCC Deposit No. PTA-4611), see attached database sheet. The DNA methyltransferase nucleic acid was expressed in a baculovirus and purified from

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High Five insect cells, see page 14, section 0127. Given the high sequence homology shared between the disclosed polynucleotide sequence and Applicants' sequences it is reasonable to conclude the encoded product is a *de novo* DNA cytosine methyltransferase polypeptide.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

14. Claims 38, 40-42 and 45-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Xie et al. (Gene 236: 87-95, 1995/ IDS reference AR, submitted January 20, 2004), and further in view of Okano et al. (Nat. Genet. 19(3): 219-220, 1998/ IDS reference AR, submitted December 17, 2004). The teachings of Xie have been presented in the 102(b) rejection. Xie does not teach the disclosed polynucleotides inserted in a recombinant vector and host cell and the method for producing a *de novo* DNA cytosine methyltransferase polypeptide by the means presented in claims 45-49.

However, Okano teaches the *de novo* DNA cytosine methyltransferase polypeptide transcripts expressed in embryonic stem (ES) cells using baculovirus expression vectors and their ability to methylate DNA substrates, see page 219, 3rd column; and page 220, first paragraph of column 1. It would have been prima

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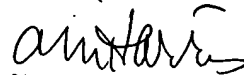
facie obvious to one of ordinary skill in the art at the time of the claimed invention was made to implement the teachings of both documents for the production of *de novo* DNA cytosine methyltransferase polypeptides. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the said teachings because Okano did effectively produce *de novo* DNA cytosine methyltransferase polypeptides.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alana M. Harris, Ph.D. whose telephone number is (571) 272-0831. The Examiner works a flexible schedule, however she can normally be reached between the hours of 7:30 am to 6:30 pm, with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



ALANA M. HARRIS, PH.D.
PRIMARY EXAMINER

Alana M. Harris, Ph.D.
07 October 2006